REMARKS

The pending claims, claims 1-15, were rejected. Claims 1, 7, and 15 have amended and new claims 16-20 have been added. Support may be found throughout the specification. No statutory new matter has been added. Reconsideration is respectfully requested.

Rejection Under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 3 and 7 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner deemed that the phrase "at least 0.25:1 preferably 0.5:1" rendered the claim indefinite because he deemed that it is unclear whether the limitations follow the phrase as part of the claimed invention.

Applicants respectfully submit that the claims as amended obviate the rejection. Therefore, the rejection under 35 U.S.C. 112, second paragraph, may be properly withdrawn.

Rejection Under 35 U.S.C. §102(b)

The Examiner rejected claims 1-10 under 35 U.S.C. §102(b) as being anticipated by Foster et al. (U.S. 6,258,341 B1). Specifically, the Examiner deemed that Foster et al. disclose a method of drying, without damage, a compound (Human zinc insulin) which is subject to deactivation on drying, or a mixture of such compound, comprising subjecting an aqueous system containing the compound or mixture to drying in the presence of one a sugar alcohol (mannitol) and at least one additive (sodium citrate) which is a glass-former or a glass formation-facilitator, whereby the compound solidifies from solution as an amorphous glass rather than forming crystals. The Examiner also rejected claims 2-9 because the limitations and/or dependability encompassed by these claims are also anticipated by Foster et al (example 3, col. 23).

Applicants respectfully submit that the present application and Foster et al. (U.S. 6,258,341) do concern glass-based stabilization of active molecules. However, there is a major difference between the present invention and that of Foster et al. Specifically, Foster et al. mainly relates to preventing clumping and stabilizing the physical dispersion of powder particles

for effective powder inhalation while the present invention relates to chemical stability of the active molecule in the glass.

It is now well established in the art that unstable compounds are stabilized if dried so as to form a solid solution in an appropriate stabilizing glass. See present specification, pages 1 through 3 and Foster et al. U.S. 6,258,341, col. 2, lines 51-67. Many of the active molecules that require stabilization are proteins and some proteins are themselves glass formers. See Foster et al. col. 13, lines 18-20. However, the act of forming a protein glass does not itself stabilize these molecules. They require to be intimately mixed with a glass of a stabilizing substance. Many materials will form stabilizing glasses. See Foster et al. col. 12, lines 25-67 and col. 13, lines 1-59 and table I. They include sugars and higher carbohydrates, inorganic chemicals such as phosphates, organic chemicals such as citrates and other carboxylates, certain amino acids and certain proteins. Substances that readily form glasses on drying from solution can assist other, co-drying, non-glass-forming substances to also form glasses possibly by inhibiting their crystallization. See Foster et al. col. 13, line 19 and page 4 of the present specification. This facilitation of glass formation requires that the facilitator molecule be present in a high proportion in the mixture often in excess of the amount of the non-glass-former. Examples 2 through 8 of Foster et al. and U.S. Pat. No. 5,589,167 describe the role of high concentrations of a glass-forming active, itself inducing glass formation in the non-glass-former mannitol.

Single substances that naturally form inert stabilizing glasses such as sugars like trehalose, sucrose or raffinose (see Foster et al. Examples 7 and 8) and in some cases citrate buffers and amino acids (see Foster et al. Examples 5 and 6) are excellent stabilizers of a very wide range of concentration of added active molecules. The latter can be present in any amount so long as there is an excess of the stabilizing glass-former for the active to be stabilized. The active can be present in tiny amounts in a vast excess of sugar glass and the active is still perfectly stabilized. These glasses are inherently very useful as the range of options available for the formulation of the actives is large. Highly potent actives which are used in small amounts can be formulated as readily as actives of low potency which need to be given in large doses. The precise concentration of stabilizing glass-former used is not critical so long as it is in excess and the formulator has many options to vary the concentration of excipients and actives. Very

adaptable glasses of this kind are highly desirable in the pharmaceutical industry.

Much less desirable glasses only stabilize at very restricted ratios between glass-forming actives and stabilizing glass. Stabilization of these actives can however, be obtained by very precise formulation, usually arrived at by trial and error, using readily crystallizable sugars or sugar alcohols such as mannitol (exemplified in U.S. Pat. No. 5,589,167 as discussed in page 5, lines 4-122 of present specification, and also in Foster et al. Examples 2, 3, 4). This is only possible if the active itself is a natural glass former and is present in high concentration, often needing to be in excess of the stabilizing mannitol. Under these circumstances the active itself acts as a glass-formation-facilitator and ensures that a stabilizing glass of mannitol is formed in intimate association with the active.

This is clearly illustrated in Foster et al. Examples 3, 4 which actually contain a huge excess (60% w/w) of the glass forming active, insulin. The effect of the precise ratio between glass forming active and stabilizing sugar is illustrated by the difference between example 1 and 2. The latter contained 20% insulin and 18.2% mannitol plus citrate buffer and glycine and stabilized well. Example 1 of Foster et al U.S. 6,258,341 also contained 20% insulin but had an excess of mannitol (66.2%) together with citrate buffer. This showed the anomalous result that the more stabilizing sugar that is present the less stable is the product and proves the role of the glass-forming facilitator for the stabilizing sugar. These considerations place sever constraints on the type of formulations that are possible and, of course they are only applicable to that small sub-set of pharmaceutically active molecules that are themselves glass formers and glass-formation-facilitators.

The present invention provides methods to form the highly desirable, adaptable non-critical glasses of sugar derivatives such as mannitol. The present invention surpasses the prior art and extends the field of non-critical adaptable glasses from single natural glass formers such as sucrose, rafinose or trehalose to complex mixtures of non-natural glass formers such as the readily crystallzable sugar alcohols like mannitol. This is achieved by the active in need of stabilization. These complex formulations form glasses whether or not an active molecule is present.

Indeed, Examples 1 through 3 of the present specification illustrate glass formation

without any actives present. These glasses can accommodate different amounts of actives and stabilize them effectively, often more effectively than the canonical glass formers like trehalose. See Figures 3 and 4. The adaptable glasses of the present invention are therefore able to contain and stabilize a wide range of types of actives, both glass formers and non-glass-formers and in a very wide range of concentrations, rather than having the severe concentration constraints as seen when the active itself is required to facilitate glass formation as in the prior art, such as in Foster et al. and U.S. Pat. No. 5,589,167.

Applicants respectfully submit that the present claims as amended are therefore novel and the rejection under 35 U.S.C. 102(b) should properly be withdrawn.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejected claims 11-15 under 35 U.S.C. §103(a) as being unpatentable over Foster et al. (U.S. Patent No. 6,258,341 B1). Specifically, the Examiner deemed that Foster et al. also disclose a method and product of elcatonin powder prepared from elcatonin and glass formers and additives.

The Examiner correctly stated that Foster et al. do not disclose the identical glass formers or additives like those claimed by Applicants. As provided above, Applicants submit that the present method as claimed is novel and produces sugar glass that, unlike the prior art, are able to contain and stabilize a wide range of types of actives, both glass formers and non-glass-formers and in a very wide range of concentrations. Therefore, one of ordinary skill in the art would not have used the method of drying of Foster et al. to prepare amorphous glass of products of compounds using the monosaccharide sugar alcohols and additives according to the present invention with a reasonable likelihood of success in obtaining suitable amorphous glass product.

The Examiner deemed that in claim 15 is obvious as Foster et al. disclose a method and product of claim 1 consisting of mannitol and other additives (example 3, col. 23). The Examiner correctly states that the difference between the present invention and that of Foster et al. is that Foster et al. do not disclose the use of dextran in combination with mannitol. Again, Applicants point out that the present sugar glasses allow one to prepare amorphous glass of products of compounds using different monosaccharide sugar alcohols and/or additives in

different percent combinations. Prior to the present invention, one of ordinary skill in the art would not have used the specific concentrations of dextran and mannitol as claimed with a reasonable likelihood of success in obtaining a suitable amorphous glass product.

Therefore, Applicants respectfully submit that the present claims as amended are nonobvious and the rejection under 35 U.S.C. 103(a) may properly be withdrawn.

Request for Interview

Applicants respectfully request either a telephonic or an in-person interview should there be any remaining issues.

Conclusion

Accordingly, in view of the foregoing amendments and remarks, the Examiner is respectfully requested to reconsider and withdrawn the rejection of the claims to allow these claims and to find this application to be in allowable condition.

Attached hereto is a marked-up version of the changes made and claims by the present amendment entitled "**Version with markings to show changes made.**"

Respectfully submitted,
JACOBSON HOLMAN PLLC

By _____
John C. Holman
Reg. No. 22,769

400 Seventh Street, N.W.
Washington, D.C. 20004-2201
(202) 638-6666
Date: September 18, 2002
Atty. Docket: 01398/P65952US0
JCH/SKS/krb

Version with markings to show changes made

1. (Amended) [A method of drying, without damage, a compound which is subject to deactivation on drying or a mixture of such compounds comprising subjecting an aqueous system containing the compound or mixture to drying in the presence of one or more monosaccharide sugar alcohols and at least one additive which is a glass-former or a glass-formation-facilitator, whereby the compound solidifies from solution as an amorphous glass rather than by forming crystals] A method for producing a dried product which is an amorphous sugar glass without crystals therein which comprises

(a) forming an aqueous system which is a solution of

(i) one or more monosaccharide sugar alcohol which would normally form sugar crystals on drying;

(ii) a compound which is normally subject to deactivation on drying, or a mixture of such compounds; and

(iii) at least one additive which is a glass-former or a formulation-facilitator, the total amount of the additive being sufficient to cause the monosaccharide sugar alcohol to form a glass on drying; wherein the additive itself does not crystallize during the drying step (b);

(b) drying the aqueous system at a temperature above its freezing point; and

(c) solidifying the components (i), (ii) and (iii) as an amorphous glass without crystals therein, whereby the amorphous glass stabilizes the compound or mixture of compounds therein and prevents damage thereto during drying.

7. (Amended) A dried product which is an amorphous glass without crystals therein, [containing] comprising one or more monosaccharide sugar alcohol and at least one additive which is a glass-former or a glass-formation-facilitator and a compound which is subject to deactivation on drying, or a mixture of such compounds, in a weight ratio of sugar alcohol plus additive to compound of at least 0.25:1 [preferably 0.5:1], the product having been dried from aqueous solution at a temperature above its freezing point.

15. (Twice amended) [A method or product according to claim 1 wherein the amorphous glass is formed from a formulation having essentially a composition selected from] A method or product according to claim 1, wherein the amorphous glass is formed from a formulation including mannitol.